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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/305,084 | 05/04/1999 | Robert J. Schneider | 5914-080-999 | 1583 |

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| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |
| ART UNIT | PAPER NUMBER |
| 1643 | |

DATE MAILED: 01/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/305,084 | SCHNEIDER ET AL. | |
| | Examiner | Art Unit | |
| | Karen A. Canella | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 33-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 33-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/19/99; 2/8/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. After review and reconsideration, the finality of the Office action of February 23, 2005 has been withdrawn.

2. Claims 33, 34, 37-39, 41 and 42 have been amended. Claims 33-42 are pending and under consideration.

3. Sections of Title 35, U.S. code not found in this action, can be found in a previous action.

4. Claims 40 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "the compound" in claim 40 lacks antecedent basis within the claim.

The recitation of "similar to" in claim 42 is vague and indefinite. Similarity is a relative term because it is interpreted differently by practitioners of the art. Therefore, without a precise definition in the specification or precise limitations within the claim, one of skill in the art would not know the cut off point where a level of E-cadherin is considered by applicant to be similar or not similar to a cell not treated with BQ788.

5. Claims 33, 37, 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kikuchi et al (Biochemical and Biophysical Research Communications, 1996, Vol. 219, pp. 734-739, reference of the IDS filed February 8, 2001) in view of Vournakis et al (U.S. 6,063,911, cited in a previous Office action).

Claim 33 is drawn in part to a method of inhibiting the progression of melanoma comprising administering to a patient in need thereof a compound that is an endothelin B receptor specific antagonist. Claim 37 embodies the method of claim 33 wherein said specific antagonist is selected from a group that includes a peptide inhibitor.

Claim 39 is drawn in part to a method of inhibiting the progression of melanoma comprising administering to a patient in need thereof a compound that is an endothelin B receptor antagonist, wherein said antagonist is selected from a group that include a peptide

inhibitor. Claim 40 embodies the method of claim 39 wherein the usefulness of said ETB of said specific antagonist is evaluated by an in vitro assay comprising contacting a cell expressing ETB and E-cadherin with endothelin and the antagonist and determining the level of E-cadherin expression, wherein if the level of E-cadherin expression is increased relative to the level of E-cadherin the absence of the antagonist, said antagonist has usefulness for the treatment of melanoma.

Claim 41 is drawn in part to a method of inhibiting the progression of melanoma comprising administering to a patient in need thereof an ETB specific antagonist selected from a group including BQ788.

Claim 42 is drawn in part to a method for inhibiting the progression of melanoma comprising administering to a patient a compound that prevents the down regulation of E-cadherin in a melanocyte-related cell, wherein said compound is a ETB specific antagonist selected from a group including a peptide inhibitor, wherein said melanocyte-related cell treated with said specific antagonist has a level of E-cadherin similar to a second melanocyte-related cell treated with BQ788, as evaluated by an in vitro assay with BQ788.

Vournakis et al teach a method of treating cancers comprising the administration of an endothelin agonist in combination with poly-N-acetylglucosamine (column 1, lines 15-30). Vournakis et al teach that melanoma is one of the few tumors to express ETB receptor that have an affinity for all three isoforms of endothelin and that said ETB receptors are expressed in primary and recurrent melanoma but the expression of ETB is decreased in metastatic melanoma (column 2, lines 46-53). Vournakis et al teach that the ETA antagonist, Ro61, inhibited melanoma proliferation in vitro (column 4, lines 45-46), and that that Ro61 is a non-specific inhibitor of both endothelin receptors, ETA and ETB (column 3, lines 44-46). Vournakis et al teach that the endothelin antagonist of BQ788 is included with the endothelin antagonists in the compositions of the invention (column 17, lines 9-19). Vournakis et al teach that a target for the poly-N-acetylglucosamine compositions of the invention is the skin (column 22, lines 59-61). Vournakis et al teach that poly-N-acetylglucosamine in combination with Ro61 delayed the death of mice carrying transplanted B16 melanoma cells and caused the complete regression of the melanoma cells in 33% of the animals after tumor injection (column 32, lines 32-41).

Vournakis et al to not teach the treatment of melanoma with poly-N-acetylglucosamine and the ETB specific antagonist of BQ788.

Kikuchi et al teach the inhibition of proliferation in primary melanoma cell lines by BQ788 (page 735 to 736, bridging sentence. Kikuchi et al teach that levels of the ETB receptor are decreased in metastatic melanoma cell lines (Table 2).

It would have been prima facie obvious at the time the invention was made to combine the ETB antagonist of BQ788 with poly-N-acetylglucosamine for the treatment of primary melanoma. One of skill in the art would have been motivated to do so by the teachings Kikuchi et al on the inhibition of primary melanoma cells lines by BQ788 and the teachings of Vournakis on targeting the poly-N-acetylglucosamine/ endothelin receptor antagonists to the skin, as well as the demonstration by Vournakis et al that Ro61 which is an antagonist for either the ETA or ETB receptor was able to inhibit the proliferation of melanoma cells. One of skill in the art would understand that the Ro61 antagonist could act through either the ETB or ETA receptors, and therefore in light of the teachings of Kikuchi et al would understand that ETB could be substituted for Ro61 in the poly-N-acetylglucosamine composition for the treatment of melanoma in a patient in need thereof. Claims 40 and 42 are included in this rejection because they require a specific antagonist of ETB selected by an in vitro assay. The selection of the antagonists by said in vitro assay is a product by process claim. Such a clam will be satisfied by the use of an antagonist that has the same structural and functional characteristics as an antagonist selected by the recited process. Accordingly, BQ788 will satisfy the structural and functional properties of a useful antagonists selected by the in vitro assays.

6. Claims 33-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the development or progression of melanoma comprising administering to a patient in need thereof a compound that is an endothelin B receptor specific antagonists, does not reasonably provide enablement for a method of preventing the initiation of melanoma comprising administering to a patient in need thereof a compound that is an endothelin B receptor specific antagonists.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

Claims 33, 37 and 39-42 are drawn in part to a method of inhibiting the development of melanoma comprising administering to a patient in need thereof a compound that is an endothelin B receptor specific antagonist. When given the broadest reasonable interpretation, the "development" of melanoma reads on the initiation of a non-malignant melanocyte which will progress to melanoma. Claims 34-36 and 38 are drawn to inhibiting the development of a melanocyte or melanocyte-related cell into melanoma. The claims clearly encompass the prevention of melanoma in a patient that is free of melanoma. Thus, the claims require that the administration of the ETB specific antagonist be given to said patient before melanoma occurs. The specification fails to teach how to determine which individuals will develop melanoma, where the melanoma will occur and the proper time at which to commence the prophylactic treatment. Further, the art teaches that the initiation of cancer is a mutational event (the abstract of Ramel et al, Environmental Science Research, 1984, Vol. 41, pp. 97-112). The specification teaches that ETB receptor antagonists inhibit the early events associated with melanoma development. However, the specification does not teach how to use the instant methods to inhibit the initiation of melanoma, because there is no nexus between the administration of the ETB antagonists and the prevention or reversal of a mutational event such that the primary initiation event in melanoma is prevented. Further, the specification does not teach how to identify a "patient in need thereof" wherein said patient is treated with the ETB antagonists before the mutational event that leads to initiation of melanoma, because said patients would be without atypical lesions because initiation, by definition, precedes progression.

7. Claims 33-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claims 33, 37 and 39-42 are drawn in part to a method of inhibiting the development of melanoma comprising administering to a patient in need thereof a compound that is an endothelin B receptor specific antagonist. When given the broadest reasonable interpretation, the "development" of melanoma reads on the initiation of a non-malignant melanocyte which will

progress to melanoma. Claims 34-36 and 38 are drawn to inhibiting the development of a melanocyte or melanocyte-related cell into melanoma. The claims clearly encompass the prevention of melanoma in a patient that is free of melanoma. The art teaches that the initiation of cancer is a mutational event (the abstract of Ramel et al, Environmental Science Research, 1984, Vol. 41, pp. 97-112). The specification teaches that ETB receptor antagonists inhibit the early events associated with melanoma development. However, there is no mechanistic nexus between inhibiting ET-1 activity at the ETB receptor and preventing a mutational event such that the primary initiation event in melanoma is prevented. One of skill in the art, upon reading of the originally filed specification would reasonably conclude that applicant was not in possession of a method of preventing melanoma initiation.

8. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

1/10/2006

KAREN A. CANELLA PH.D
PRIMARY EXAMINER